

BCG and COVID-19: Implications for South Africa

The anecdotal evidence for a positive impact of Bacille Calmette Guerin (BCG) vaccine on COVID-19 disease comes from an ecological study in which morbidity and mortality rates from COVID-19 in various countries are compared in relation to their use of BCG vaccine in the past (Miller et al, medRxiv preprint doi: <https://doi.org/10.1101/2020.03.24.20042937>; not peer reviewed). The authors suggest that countries with well-established BCG vaccination programmes have better outcomes compared to countries without such programmes.

What are the implications for South Africa?

BCG vaccine was first used in 1921 to prevent tuberculosis. The original BCG vaccine was not cloned but was distributed to a number of laboratories worldwide. This has resulted in a number of related BCG vaccines with varying phenotypic and genomic characteristics – the point is that not all BCG vaccines are the same. The five main strains used in the last 2-3 decades, accounting for more than 90% of the world's production, are the Tokyo, Russian, Danish, Pasteur and Moreau strains. These strains also induce varying immunological responses and potentially also variable protective efficacy against pulmonary TB. The estimates from clinical trials range from 0-80% with an average protection rate of only 50%. BCG does, however, protect against the more severe forms of TB in infancy, including miliary TB and tuberculous meningitis. Meta-analyses of published studies report that protection is of the order of at least 80%. BCG vaccine also protects against leprosy and provides some protection against Buruli ulcer caused by *M. ulcerans*.

Somewhat controversial evidence suggests that newborn BCG vaccination may improve overall infant survival, independent of protection against TB, through “heterologous” or nonspecific protection against respiratory infections in early infancy, by the mechanism of “trained immunity” (Moorlag et al, *Clinical Microbiology and Infection* 2019). This hypothesis is suggested by Miller et al as a possible reason why BCG vaccination might protect against COVID-19.

In South Africa, BCG has been used sporadically since the early fifties and was first administered to school-going children. However, from 1973 BCG has been given universally to all newborn infants with very high coverage. Therefore, South African adults aged 45 years old or younger probably received BCG vaccine (these will include large numbers of our health work force) and those between 45 - 65 years possibly received BCG, but it is unlikely that those older than 65 years of age received BCG vaccine. Given that the non-specific beneficial effects of newborn BCG vaccination are thought to be short-lived and limited to early infancy, it seems unlikely that programmatic BCG vaccination of South African infants might confer long-term protection against COVID-19 mortality that mainly affects the elderly.

A related question is whether older South African adults, who may not have received BCG vaccination in infancy or childhood, should be vaccinated with BCG to possibly prevent or mitigate the severity of COVID-19 infections as suggested by Miller et al.

The first point to note is that ecological studies such as the one by Miller et al do not prove causality and we have to be mindful of the potential for over-interpretation of results and generation of potentially spurious findings from such studies. There are also problems in how

the authors interpret the data. For example, other important factors that might lead to major differences in COVID-19 infection and mortality rates in countries with high vs low BCG vaccination coverage, such as socio-demographic factors, season, climate, COVID-19 testing rate, and the relative “maturity” of the country-level COVID-19 epidemic, are not evaluated as potential confounders.

It should be noted that there are no data to confirm whether BCG vaccine is safe in older adults. Using any vaccine in the elderly needs to be studied to ensure that it is safe and does not cause problems. BCG vaccine is a live attenuated vaccine and should definitely not be administered to individuals who are immunocompromised as it can lead to significant complications. The ageing process is also associated with a decline in immune functioning in general (called immunosenescence) and thus there may be issues with using a vaccine like BCG in this age group.

It is also likely that >80% of older South African adults will have been exposed and asymptotically infected with “latent” TB during their lifetime. Since TB is a mycobacterium very similar to BCG vaccine, and latently infected people show similarities in immune response to BCG-vaccinated people, it seems unlikely that BCG vaccination of older adults would offer additional non-specific protection against COVID-19. It is conceivable that BCG revaccination of adolescents and young adults without latent TB infection might offer some non-specific benefit against COVID-19. This hypothesis can be tested retrospectively in an ongoing South African trial (BCG REVAX), which is currently paused to recruitment due to the COVID-19 lockdown.

BCG vaccine administered to an individual who has been previously infected with tuberculosis may result in a significant adverse reaction at the site of vaccination. This is important in the SA context where exposure to tuberculosis is virtually universal and infection rates are extremely high.

The bottom line is that there is insufficient evidence that BCG vaccination of South African adults will impact on COVID-19 morbidity and mortality. In addition, there is no evidence to indicate that BCG vaccination is safe in older populations. If we are to consider using BCG in the COVID-19 pandemic in South Africa then this first needs to be subjected to a clinical trial to generate evidence.

The current mainstay for prevention of COVID-19 remains social distancing, cough hygiene and hand washing.

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